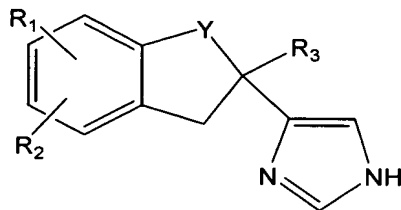


PROCESS FOR PREPARING SUBSTITUTED IMIDAZOLE DERIVATIVES AND INTERMEDIATES USED IN THE PROCESS

FIELD OF THE INVENTION

- 5 The present invention relates to a new process for preparing substituted imidazole derivatives of formula (I) and acid addition salts thereof,



(I)

- 10 in which formula Y is -CH₂- or -CO-, R₁ is H, halogen or hydroxy, R₂ is H or halogen and R₃ is H or lower alkyl.

The invention also relates to intermediates used in the process and to their preparation.

15 BACKGROUND OF THE INVENTION

- The compounds of the above-mentioned formula (I) are highly selective and long-acting antagonists of α_2 -adrenoceptors and they have a good peroral bioavailability. The compounds are especially valuable in the treatment of cognitive disorders. Compounds of formula (I) have been
- 20 described in patent publication EP 0 618 906 B1. Specific examples of such compounds are 4-(2-ethyl-5-fluoroindan-2-yl)-1H-imidazole and 4-(5-fluoroindan-2-yl)-1H-imidazole.

- The above-mentioned publication EP 0 618 906 B1 also discloses methods of preparing compounds of formula (I). Said methods relate to various
- 25 ways of modifying the substituents in the benzene moiety of the indan ring system. There is no disclosure of a total synthesis, which would lead to the desired compounds in good yield.

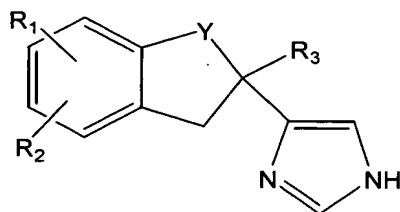
- Publication EP 0 310 745 B1 discloses a process for preparing compounds of formula (I), wherein the last step of the process comprises the
- 30 use of formamide for the formation of the imidazole ring. The use of formamide, however, requires severe reaction conditions, which should be avoided in connection with industrial production in large scale.

Although the individual steps of the process according to the present invention are known as such (see e.g. EP 0 146 228 B1), it has now surprisingly been found that compounds of formula (I) can be prepared, also in large scale, in very good yields by using the synthesis route described below.

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SUMMARY OF THE INVENTION

The present invention relates to a process for preparing substituted imidazole derivatives of formula (I) and acid addition salts thereof



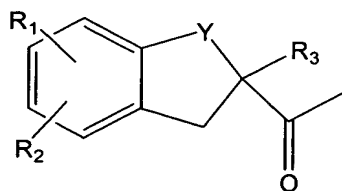
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(I)

in which formula Y is $-\text{CH}_2-$ or $-\text{CO}-$, R_1 is H, halogen or hydroxy, R_2 is H or halogen and R_3 is H or lower alkyl, comprising the steps of

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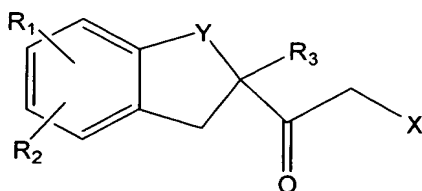
a) halogenating a compound of formula (II)



(II)

wherein Y, R_1 , R_2 and R_3 are as defined above, to obtain a compound of formula (III)

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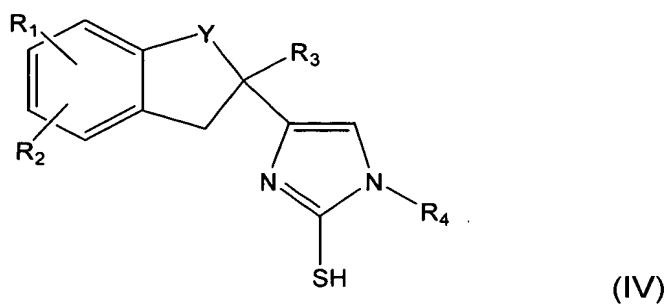


(III)

wherein Y, R_1 , R_2 and R_3 are as defined above and X is halogen,

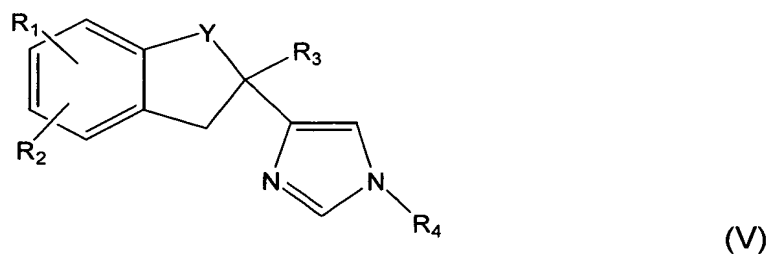
b) reacting the compound of formula (III) thus obtained with an amine of formula R_4NH_2 , wherein R_4 is an easily removable leaving group, and an alkali metal thiocyanate, to obtain a compound of formula (IV)

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wherein Y, R₁, R₂, R₃ and R₄ are as defined above,

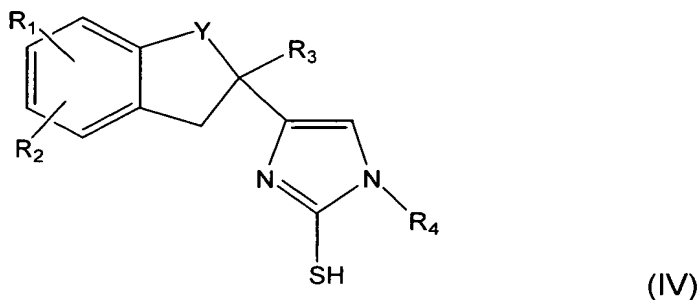
- c) removing the mercapto group from the compound of formula (IV) to obtain a
 5 compound of formula (V)



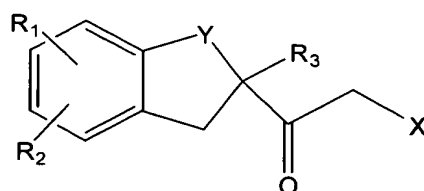
wherein Y, R₁, R₂, R₃ and R₄ are as defined above,

- d) removing the group R₄ from the compound of formula (V) to obtain a
 10 compound of formula (I), and, if desired,
 e) converting the resulting compound of formula (I) into an acid addition salt thereof.

- Further the invention relates to a process for preparing a
 15 compound of formula (IV)



- wherein Y is -CH₂- or -CO-, R₁ is H, halogen or hydroxy, R₂ is H or halogen
 20 and R₃ is H or lower alkyl, comprising reacting a compound of formula (III)



(III)

wherein Y, R₁, R₂ and R₃ are as defined above and X is halogen, with an amine of formula R₄NH₂, wherein R₄ is an easily removable leaving group, and
 5 an alkali metal thiocyanate.

The invention also relates to intermediate compound (IV) wherein Y, R₁, R₂, R₃ and R₄ are as defined above.

DETAILED DESCRIPTION OF THE INVENTION

10 In this context, the term *an acid addition salt* refers to an addition salt of any pharmaceutically acceptable acid, preferably hydrochloric or hydrobromic acid.

In this context, the term *halogen* refers to F, Cl, Br and I. Regarding R₁ and/or R₂ it preferably refers to F and/or Cl, and most preferably to F.
 15 Regarding X it preferably refers to Cl and Br, and most preferably to Br.

In this context, the term *lower alkyl* refers to a monoradical branched or unbranched saturated hydrocarbon chain having from 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms and most preferably 1 or 2 carbon atoms.

20 In this context the term *aralkyl* refers to substituted or unsubstituted groups *-alkylene-aryl*. *Alkylene* refers to a diradical of a branched or unbranched saturated hydrocarbon chain, preferably having from 1 to 10 carbon atoms and more preferably having 1 to 6 carbon atoms and *aryl* refers to an unsaturated aromatic carbocyclic group of from 6 to 20 carbon atoms
 25 having a single ring (e.g. phenyl) or multiple condensed (fused) rings (e.g. naphthyl or anthryl).

In this context the term *easily removable leaving group* refers to any group that a person skilled in the art would know to be easily removable. Preferred *easily removable leaving groups* would be aralkyls, e.g. benzyl.

30 According to the present invention a compound of formula (II) is, in step a), halogenated with a halogenating agent to obtain a compound of formula (III), where X is a halogen, e.g. Br, Cl or I. A preferred halogenating agent is Br₂. The reaction is suitably carried out in a solvent, such as an

alcohol, e.g. methanol, at room temperature or below. A suitable temperature is -8°C to $+25^{\circ}\text{C}$, preferably -8°C to -5°C .

In step b) the compound of formula (III) obtained in step a) is reacted with an amine of formula R_4NH_2 where R_4 is a easily removable
5 leaving group, and an alkali metal thiocyanate to obtain a mercapto compound of formula (IV). The reaction is suitably carried out in a solvent, such as an alcohol, e.g. ethanol or butanol, at an elevated temperature, preferably at reflux temperature. The amine for the reaction may be one where R_4 is aralkyl, preferably benzyl. A preferred alkali metal thiocyanate is potassium thiocyanate.

10 In step c) the mercapto group is removed from the compound of formula (IV) obtained in step c) to obtain a compound of formula (V). The reaction is suitably carried out in the presence of a catalyst, e.g. Raney-Nickel, at a temperature of 40°C to 90°C , preferably 40°C to 60°C .

15 In step d) the group R_4 can be removed from the compound of formula (V) obtained in step c) by treating the compound of formula (V) with ammonium formate in the presence of a catalyst, such as Pd/C. Alternatively a catalyst, such as Raney-Nickel, may be used, or R_4 may be removed by hydrogenation in the presence of Pd/C.

20 The resulting compound of formula (I) may be converted into acid addition salts using methods known per se. Preferred acid addition salts are HCl and HBr.

Preferred compounds of formulae (I) to (V) are those where Y is CH_2 , R_1 is F, R_2 is H and R_3 is ethyl.

25 The process according to the present invention makes it possible to prepare compounds of formula (I) in good yield and in a simple way, e.g. by using lower reaction temperatures, that also are suitable for large-scale production. The known methods result in poor yields and require severe reaction conditions, e.g. high temperatures, which makes large-scale production difficult. For instance, compared to the process using formamide
30 (EP 0 310 745 B1), the process of the present invention using lower temperatures does not create separation or isolation problems relating to great amounts of various impurities that are typically formed in the known formamide process

35 The following examples illustrate the invention, but are not intended to restrict the scope of the invention.

Example 1**2-bromo-1-(2-ethyl-5-fluoro-indan-2-yl)-ethanone**

3,8 g of 2-acetyl-2-ethyl-5-fluoroindan and 35 ml of methanol were
5 placed into a round-bottomed flask equipped with a thermometer, a
mechanical stirrer and a dropping funnel. The reaction mixture was cooled in a
cooling bath while stirring to a temperature between -5°C and -8°C and
0,7 ml of a Br_2 -solution in a small amount of methanol was added dropwise.
The cooling bath was removed and the reaction mixture was stirred at room
10 temperature for 2 hours. The reaction mixture was cooled to a temperature
between -5°C and -8°C and an additional 0,175 ml of Br_2 -solution in a small
amount of methanol was added dropwise. The cooling bath was removed and
the reaction mixture was stirred at room temperature for an additional 1 to 2
hours. After chromatographic purification using methylene chloride as an
15 eluent 2,51 g of 2-bromo-1-(2-ethyl-5-fluoro-indan-2-yl)-ethanone was obtained
as a liquid (yield 69 %).

^1H NMR (200 MHz, CDCl_3 , ppm): 0.85 (3H, t, J 7.6 Hz, CH_2CH_3), 1.82 (2H, q,
J 7.5 Hz, CH_2CH_3), 2.83-2.93 (2 H, dd, the indan ring H2-1 or H2-3), 3.32-
20 3.46 (2 H, dd, the indan ring H2-1 or H2-3), 4.11 (2H, s, $\text{CH}_2\text{-Br}$), 6.79-7.10
(3H, m, Ar-H)

HPLC-MS: 285-286-287 (68, M^+ , Br-isotopes), 205 (72), 187 (100).

UV (Lambda-max): 208 nm (Abs. 1.01020 AU), 271 nm (Abs. 0.27428 AU),
277 nm (Abs. 0.27026 AU).

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Example 2**1-benzyl-5-(2-ethyl-5-fluoro-indan-2-yl)-imidazole-2-thiol**

1,62 g of 2-bromo-1-(2-ethyl-5-fluoro-indan-2-yl)-ethanone was
30 dissolved in 25 ml of ethanol in a glass round-bottomed flask equipped with a
mechanical stirrer, a thermometer and a dropping funnel. The reaction mixture
was heated to reflux temperature while stirring. 0.366 g of benzylamine
dissolved in 5 ml ethanol was added slowly in a drop-wise fashion to the
solution. After the addition of benzylamine the mixture was refluxed for one
35 hour. 0,330 g of potassium thiocyanate was added portionwise during 30
minutes and the reaction mixture was refluxed for 2 hours. The reaction

mixture was evaporated to dryness before 150 ml ethyl acetate was added and the solution was washed with water. The organic phase was dried over Na_2SO_4 , filtered and evaporated providing 1,13 g of 1-benzyl-5-(2-ethyl-5-fluoro-indan-2-yl)-imidazole-2-thiol (yield 31 %). The analytical sample was
 5 purified using TLC-plates. The purity was measured by HPLC: 62 %. Normally the crude product was used in the following step.

^1H NMR (200 MHz, CDCl_3 , ppm): 0.75 (t, CH_2CH_3), 1.80 (q, CH_2CH_3), 2.81-3.30 (m, the indan ring H_2 -1 and H_2 -3), 5.18 (s, $\text{N-CH}_2\text{-Ar}$), 6.24 (s, $-\text{SH}$), 6.77-7.09 (m, Ar-H, im-H), 7.23-7.36 (m, Ar- $\text{H-CH}_2\text{-N}$).
 10 HPLC-MS: 353 (100, M^+), 221 (29), 187 (12).

Example 3

1-benzyl-5-(2-ethyl-5-fluoro-indan-2-yl)-imidazole

15

7,5 ml of Raney-Nickel prepared according to Vogel, Practical Organic Chemistry, 5th Edition, 1999, Longman, U.K. p. 450-451, was mixed with 20 ml of ethanol under nitrogen atmosphere in a round-bottomed flask equipped with a thermometer and a stirring bar. 500 mg of 1-benzyl-5-(2-ethyl-5-fluoro-indan-2-yl)-imidazole-2-thiol was dissolved in 10 ml of ethanol and
 20 added to the mixture. The reaction mixture was stirred at 40 °C for about 10 hours and then the temperature was raised to 60 °C for 2 hours followed by cooling to room temperature. The mixture was filtered and the filter (CeliteTM) was washed with ethanol. The ethanol solution was evaporated to dryness to
 25 obtain 151 mg of a crude product. After chromatographic purification using methylene chloride, methylene chloride:methanol (10:1) and methylene chloride:methanol (1:1) as eluents 1-benzyl-5-(2-ethyl-5-fluoro-indan-2-yl)-imidazole was obtained. The purity was measured by HPLC: 83 %.

30 ^1H NMR (200 MHz, MeOD, ppm): 0.70 (3H, t, CH_2CH_3), 1.82 (2H, q, CH_2CH_3), 2.90-3.01 (2 H, dd, the indan ring H_2 -1 or H_2 -3), 3.13-3.25 (2 H, dd, the indan ring H_2 -1 or H_2 -3), 5.10 (2H, s, $\text{N-CH}_2\text{-Ar}$), 6.72-6.87 (3H, m, Ar-H, im-H), 7.05-7.18 (3H, m, Ar-H, Ar- $\text{H-CH}_2\text{-N}$), 7.29-7.32 (3H, m, Ar- $\text{H-CH}_2\text{-N}$), 7.56 (1H, s, im- H).

35 HPLC-MS: 321 (100, M^+).

Example 4**4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole**

53 mg of 1-benzyl-5-(2-ethyl-5-fluoro-indan-2-yl)-imidazole, 20 mg
5 of Pd/C, 51 mg of ammonium formate and 2 ml of ethanol were added under
nitrogen atmosphere into a round-bottomed flask equipped with a thermometer
and a stirring bar. The reaction mixture was stirred at reflux temperature for 6
hours. The mixture was filtered and the filter (Celite™) was washed with
ethanol. The reaction mixture was placed back into a round-bottomed flask and
10 an additional 20 mg of Pd/C and 51 mg of ammonium formate were added
under nitrogen atmosphere. The mixture was heated to reflux temperature and
refluxed for 2 hours. Then the mixture was cooled to room temperature and
filtered. The filter (Celite™) was washed with ethanol and after evaporation to
dryness, whereby 4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole was obtained.
15 The analytical sample was purified using TLC-plates. The purity was measured
by HPLC: 60 %. Normally the crude product was used in the following step.

1H NMR (200 MHz, MeOD, ppm): 0.76 (t, CH₂CH₃), 1.29 (q, CH₂CH₃), 2.98-
3.22 (m, the indan ring H₂-1 and H₂-3), 6.78-6.94 (m, Ar-H, im-H), 7.09-7.19
20 (m, Ar-H, im-H).
HPLC-MS: 231 (100, M+).

Example 5**4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole**

25

10 ml of the crude product obtained in Example 3 was placed in a
round-bottomed flask equipped with a thermometer and a stirring bar. 1,5 ml of
Raney-Nickel in ethanol (Raney-Nickel prepared according to Vogel, Practical
Organic Chemistry, 5th Edition, 1999, Longman, U.K. p. 450-451), was added
30 under nitrogen atmosphere. The reaction mixture was stirred at reflux
temperature for about 14 hours. After filtration and evaporation crude 4-(2-
ethyl-5-fluoro-indan-2-yl)-1H-imidazole was obtained.

HPLC-MS: 231 (100, M+).
35

Example 6**4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole-hydrochloride**

A HCl/methanol reagent was prepared by bubbling HCl-gas through
5 methanol. 100 mg of 4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole was
dissolved in 2 ml methanol in a round-bottomed flask. 2 ml of HCl/methanol
reagent (3 M) was added slowly to the solution while stirring. During the
addition the internal temperature of the mixture was kept below 29 °C by
cooling. The resulting mixture was evaporated at a temperature between 35 °C
10 and 40 °C to viscous colourless oil whereupon it was dissolved in 2 ml of
acetone at the same temperature. The solution was cooled to a temperature
between 10 °C and 15 °C at which temperature the mixture started to
crystallize. The crystalline material was filtered, washed with cooled acetone
and dried in a vacuum oven at 35 °C overnight. A second crop was isolated
15 from the mother liquid followed by cooling, filtering and drying as described
above. The yield of 4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole-hydrochloride
was altogether 87% of the theoretical, m.p. 171 – 173 °C.